



PATENT
Docket No.: 1662/49502

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

APPLICANT : SINGER ET AL.
SERIAL NO. : 09/552,485
FILING DATE : April 18, 2000
FOR : NOVEL SYNTHESIS AND CRYSTALLIZATION OF
PIPERAZINE RING-CONTAINING COMPOUNDS
GROUP ART UNIT : 1624
EXAMINER : K. Habte

Address to:
Assistant Commissioner for Patents
Washington D.C. 20231

SECOND DECLARATION OF JUDITH ARONHIME

I, JUDITH ARONHIME, Ph.D., of Harav Maor Josef 5a, Rehovot Israel, having been warned that I must state the truth or be liable to the penalties prescribed by law for failure to do so, declare as follows:

1. I have worked for Teva Pharmaceutical Industries, Ltd. ("Teva") since January 1991. Since then I have been in charge of the solid state characterization laboratory at Teva. I received the Ph.D. degree from the Casali Institute of Applied Chemistry, the Hebrew University of Jerusalem in 1989. As head of the solid state characterization laboratory I have continued to study and use known techniques of solid state characterization and to use them to develop specific methods for the identification and quantification of compounds of interest. In our laboratory we have characterized the solid state properties of over 30 drugs and drug products. I supervise five coworkers. Teva has and continues to invest in state-of-the-art equipment to carry out these solid state characterizations at Teva's solid state characterization laboratory in Israel.

2. Unless otherwise stated, I have personal knowledge of the solid state characterization of the materials discussed below: I either carried out or supervised these characterizations.
3. I have read and understood the specification and claims of the above-captioned patent application entitled "Novel Synthesis and Crystallization of Piperazine Ring-containing Compounds".
4. I have read and understood the attached uncertified translation of published PCT Application WO 01/38330. This publication describes a process for preparing a mirtazapine hydrate intermediate. Example 8 describes dissolving crude mirtazapine in methanol, treating with decolorizing charcoal, and filtering and washing the charcoal. Water was then added dropwise to the solution at 0-10 °C. The resulting mirtazapine hydrate crystals were dried under reduced pressure at 50-60 °C until the moisture content was below 3.5 weight %. The X-ray diffraction pattern is shown in Figure 3.
5. I understand that Claude Singer (see attached Singer Declaration, Exhibit 1) conducted an experiment in which an adduct of mirtazapine and water was prepared according to Example 6 of the above-captioned application, which states, in relevant part, the following:

Mirtazapine (20 g), obtained as in Examples 2 and 3, is suspended in 20 mL of ethanol and heated to reflux. At reflux, 40 mL of water is added dropwise to the solution over one hour followed by cooling to 10° C. The resulting filter cake is washed with a solution of water:ethanol (2:1) and dried at 60° C under a vacuum.
6. The X-ray diffraction results of the mirtazapine adduct obtained in the preceding paragraph was ascertained immediately before (3.2% water) and after (0.2% water) the drying step. These X-ray diffraction results are attached as Exhibit 2.

7. In my professional opinion, the X-ray diffraction results of the mirtazapine hydrate shown in Figure 3 of the published PCT application and of the mirtazapine adduct shown in Exhibit 2, both before and after drying, are all substantially the same. I therefore conclude that these three crystalline forms are substantially identical.
8. I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and believe are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the application or any patent issuing thereon.

Dated: _____

Signed _____

Judith Aronhime, Ph.D.